



# Statins and cardiovascular disease outcomes: before and during the COVID-19 pandemic (SCOBAC): meta-analysis and systematic review of large populations

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**Background:** Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide, both due to heart and vascular disease. In Indonesia alone, 470,000 deaths are estimated each year due to CVD. Based on the latest guideline, statins are highly recommended in the prevention of CVD.

**Objective:** To assess the role of statins in reducing CVD rates, and all-cause mortality, before and during the COVID-19 pandemic respectively.

**Methods:** Literature search was performed from 1994 – 2021. Data extraction was in the form of Major Adverse Cardiac Events (MACEs) before the pandemic, and all-cause mortality, before and during the COVID-19 pandemic. Literature of medical database extracted based on inclusion and exclusion criteria. The research analyzed two study designs: clinical trials for pre-pandemic and observational studies for pandemics.

**Results:** After critical appraisal, 23 clinical trials and 9 observational studies were included in the data analysis. Statins played a role in reducing MACEs before the pandemic (OR: 0.62,  $p < 0.05$ , 95% CI 0.60 – 0.74,  $I^2 = 91\%$ ). However, there was no significance between the groups receiving statins and those without statins in reducing mortality during the pandemic (RR: 0.97,  $p > 0.05$ , 95% CI 0.90 – 1.04).

**Conclusion:** Statins have been shown to statistically reduce mortality before the COVID-19 pandemic and further studies are needed during the pandemic. Government policies need to consider the lack of screening for dyslipidemia and appropriate statin treatment in the primary care setting, especially during the pandemic.

**Keywords:** Cardiovascular Disease, COVID-19 MACEs, Mortality, statins.

## INTRODUCTION

The major leading cause of morbidity and mortality worldwide is attributed to cardiovascular disease (CVD). Cardiovascular diseases are responsible for the majority of non communicable disease mortality globally (17.9 million individuals) each year. In Indonesia alone, 470,000 deaths are estimated each year due to CVD.<sup>1-3</sup>

During the COVID-19 pandemic, there is evidence to suggest that cholesterol biosynthesis pathways play an important role in the assembly, replication and infectivity of these viral particles.<sup>4,6</sup> Cholesterol concomitantly traffics angiotensinogen converting enzyme (ACE2) to the endocytic entry site where SARS-CoV-2 presumably docks to efficiently exploit entry into the cell. Furthermore, in cells producing virus, cholesterol optimally positions furin for priming SARS-CoV-2, producing a more infectious virion with improved binding to the ACE2 receptor.<sup>7,8</sup>

Statin treatment has been demonstrated to be extremely helpful for both primary and secondary CVD prevention.

Based on the recommendations of the ESC/EAS 2019 and the ESC Guidelines on CVD Prevention 2021, statins are highly recommended in the prevention of CVD.<sup>4,5</sup> The American College of Cardiology and American Heart Association (ACC/AHA) recommendations for 2013 recommend the use of statins for adults to lower the incidence of cardiovascular adverse events.<sup>1,5</sup> In addition, it is also known that statins might have a role in antiviral activity.<sup>9</sup> This study aimed to assess the role of statins in reducing CVD rates, and all-cause mortality, before and during the COVID-19 pandemic respectively.

## METHODS

This study followed the Cochrane Collaboration standards and was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension (PRISMA). Literature search was performed from 1994 – 2021. Data extraction was in the form of Major Adverse Cardiac Events (MACEs) before the pandemic, and all-cause mortality, before and during the COVID-19 pandemic.

Search strategy string using PRISMA applied in various databases were: 1) Pubmed: (((statin) OR (HMG-CoA reductase inhibitor)) AND (cardiovascular disease))) NOT ((coronary heart disease) NOT ((myocardial infarction))). 2) ScienceDirect: statin W/15 cardiovascular disease AND mortality NOT cancer. 3) Cochrane Library: (statin OR simvastatin OR atorvastatin) AND “cardiovascular disease” NOT “coronary heart disease”

Literature of medical database extracted based on inclusion and exclusion criteria. The PICO for the study were: Population includes patients at risk for cardiovascular disease (dyslipidemia, heart failure). Intervention for statin class drugs, and the comparison for Placebo and other non-cholesterol lowering drugs. Outcomes were Cardiology outcomes for MACEs (defined as cardiovascular mortality, non-fatal myocardial infarction, or coronary revascularization procedure), and all-cause mortality.

Inclusion criteria: 1. The studies involved used English or Indonesian Language, 2. The study design used was observational studies for the pre-pandemic section and clinical trials during the pandemic, 3. The trial drugs or medications used are statins, such as simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin etc, 4. Data related to cardiovascular disease events, and all-cause mortality, both before and during the pandemic, 5. The comparison used can be a placebo, other drugs or without statin

Exclusion criteria: 1. The study used presents incomplete data, 2. Patients enrolled with myocardial infarction in the baseline, 3. Retracted studies.

Quality of articles were assessed using Jadad score and STROBE (The Strengthening and Reporting of Observational Studies in Epidemiology). The risk of bias of the included studies was assessed using the Cochrane risk bias tools (Review Manager 5.4 provided by the Cochrane Collaboration).

The selection of studies was done and agreed upon by all reviewers, and screening for duplicates were done automatically using citation manager software *Mendeley*. If there were matters that become disputed, AJ and JAT act as third parties who make decisions. Analysis of data for outcome were performed using the program *Review Manager 5.4*, calculating for measurement effect, generating funnel plot, and *Forest Plots*. Efek pengukuran yang dipakai dalam analisis ini adalah Risk Ratio untuk studi eksperimental dan odds ratio untuk studi observasioanl.

Heterogeneity was calculated using the chi square test (Cochran’s Q/Q Test), if the value was below 0.05, indicating that there was a difference between studies or statistically heterogeneity between studies was significant. Interpretation is also taken from the value of I2, which indicates the percentage of total variation between studies not caused by chance factors. If the value of I2 = 0, it indicates no variation

at all. An I2 value below 50% is still considered to be a small variation between studies, that is, it is homogeneous.

## RESULTS

Literature search results obtained 1034 non-duplicate studies citations. The 879 articles are excluded after title/abstract screen and 155 articles retrieved. During the search for the title, it is focused on the research questions that have been agreed upon at the beginning. During data extraction and full text screening 124 articles do not satisfy the inclusion criteria and were excluded. This includes a total of 12 downloaded studies that were Excluded after careful reading.<sup>10-21</sup> Studies that did not control for confounding variables were excluded. After critical appraisal and agreement by the team with AJ and JAT as third parties, 23 clinical trials and 9 observational studies were obtained and involved in data analysis.

In figures 2, 3 and 4, the funnel plots show symmetrical results. Studies with greater precision had a narrow spread and clustered at the top, whereas studies with less power in estimating the effect of precision clustered at the bottom. This funnel plot shows that studies with greater precision estimate close to the true effect, in this case the RR value is slightly below 1. In this funnel plot, studies with small precision have large variability, but the distribution remains symmetrical.

Regarding the heterogeneity test, each forest plot in figure 5, figure 6, figure 7 shows similar results. Both from the Q test, the value of  $p < 0.05$ , and the value of I2, almost 100%, except for figure 6. The results of the heterogeneity test in this analysis show that the estimates of the individual studies have different magnitudes, or minimal different directions. In other words, there is little variation between subjects.

The results of the heterogeneity test as the basis for selecting the method in calculating the pooled estimate, the

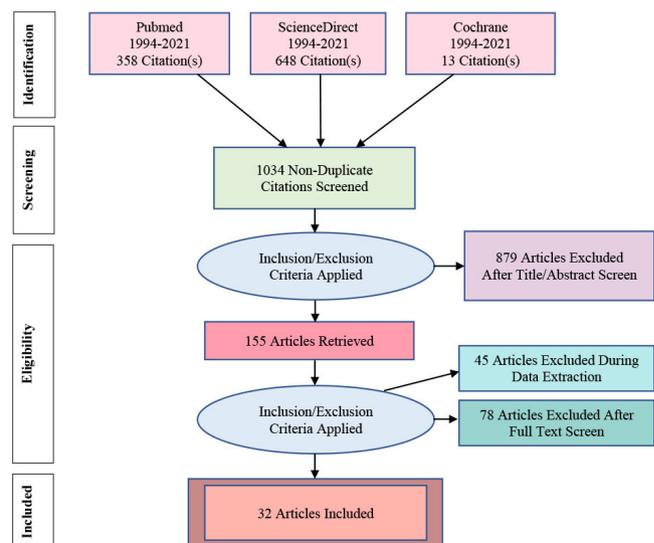


Figure 1. Flow chart of studies.

**Table 1. Studies included from before the COVID-19 pandemic**

<i>Study</i>	Furberg <sup>22</sup>	Scandinavian Simvastatin Survival Study <sup>23</sup>	Salonen <sup>24</sup>	Shepherd <sup>25</sup>	Mercuri <sup>26</sup>	Sacks <sup>27</sup>	Downs <sup>28</sup>	
<i>Year</i>	1994	1994	1995	1995	1996	1996	1998	
<i>Trial drug</i>	Lovastatin 20-40mg	Simvastatin 20mg	Pravastatin 40mg	Pravastatin 40mg	Pravastatin 40mg	Pravastatin 40mg	Lovastatin 20-40 mg	
<i>No. of subject</i>	6595	4444	447	6595	305	4159	6605	
<i>Type of patients</i>	Carotid Atherosclerosis	Angina Pectoris or Previous MI	Hypercholesterolemia	Hypercholesterolemia	Hypercholesterolemia	Hypercholesterolemia or Previous MI	Outpatient	
<i>Study</i>	LIPID Study <sup>29</sup>	MRC/BHF <sup>30</sup>	Shepherd <sup>31</sup>	Asselbergs <sup>32</sup>	Zanchetti <sup>33</sup>	Lemos <sup>34</sup>	Stegmayr <sup>35</sup>	Knopp <sup>36</sup>
<i>Year</i>	1998	2002	2002	2004	2004	2005	2005	2006
<i>Trial drug</i>	Pravastatin 40mg	Simvastatin 40mg	Pravastatin 40mg	Pravastatin 40mg	Pravastatin 40mg	Fluvastatin 2x40mg	Atorvastatin 10mg	Atorvastatin 10mg
<i>No. of subject</i>	9014	20536	5804	864	508	1358	143	2,410
<i>Type of patients</i>	Angina Pectoris or Previous MI	Previous coronary/arterial disease, or diabetes	History or risk of vascular disease	Microalbuminuria	Hypertensive & Hypercholesterolemic with Asymptomatic Carotid Atherosclerosis	Normal and mild renal impairment	Severe Chronic Kidney Disease	Diabetes mellitus
<i>Study</i>	Nakamura <sup>37</sup>	Neil <sup>38</sup>	SPARCL <sup>39</sup>	Kjekshus <sup>40</sup>	Sever <sup>41</sup>	Soveri <sup>42</sup>	Glynn <sup>43</sup>	Han <sup>44</sup>
<i>Year</i>	2006	2006	2006	2007	2008	2009	2010	2017
<i>Trial drug</i>	Pravastatin 5-20mg	Atorvastatin 10mg	Atorvastatin 80mg	Rosuvastatin 10mg	Atorvastatin 10mg	Fluvastatin 40mg	Rosuvastatin 20mg	Pravastatin 40mg
<i>No. of subject</i>	8214	2838	4731	5011	10 305	1706	17802	2867
<i>Type of patients</i>	Hypercholesterolemia	Diabetes Mellitus	Previous stroke or transient ischemic attack	Systolic heart failure	Hypertension	Renal transplant recipients	>70 years old with elevated C-Reactive Protein	Hypertension with Coronary Heart Disease Risk

**Table 2. Studies included in the COVID-19 pandemic era**

<i>Study</i>	Alamdari <sup>45</sup>	Butt <sup>46</sup>	Gupta <sup>47</sup>	Krishnan <sup>48</sup>	Masana <sup>49</sup>	Nicholson <sup>50</sup>	Saeed <sup>51</sup>	Song <sup>52</sup>	Zhang <sup>53</sup>
<i>Year</i>	2020	2020	2020	2020	2020	2020	2020	2020	2020
<i>No. of subject</i>	459	4842	1296	152	2157	1040	4252	249	4305
<i>Type of patients</i>	COVID-19	COVID-19	COVID-19	COVID-19	COVID-19	COVID-19	COVID-19	COVID-19	COVID-19

method chosen is the fixed effect model. For outcomes in the form of MACE and mortality before the covid era, showing the role of statins is very important, p value <0.05 (figure 5

and figure 6). However, not in the covid era, the p value > 0.05 (figure 7).

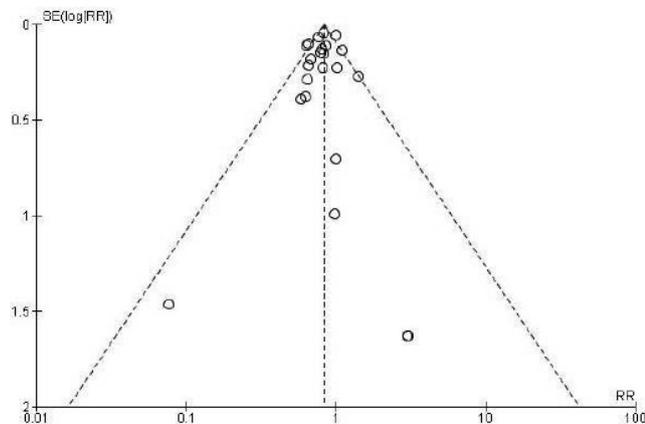
## DISCUSSION

The evidence on the benefits of statins has led clinicians to promote their use on a global scale. In secondary prevention, evidence strongly suggests that the use of statins is associated with a reduction in the risk of all-cause mortality, cardiovascular events, and cardiovascular mortality.<sup>54,55</sup> With the recommendation of the 2016 European Society of Cardiology/European Society of arteriosclerosis (ESC/EAS) guidelines, the status of statins as the cornerstone of lipid-lowering drugs remains solid, especially in the secondary prevention of CVD in high-risk individuals. The current evidence now also supports the benefits of statins for primary prevention.<sup>56</sup>

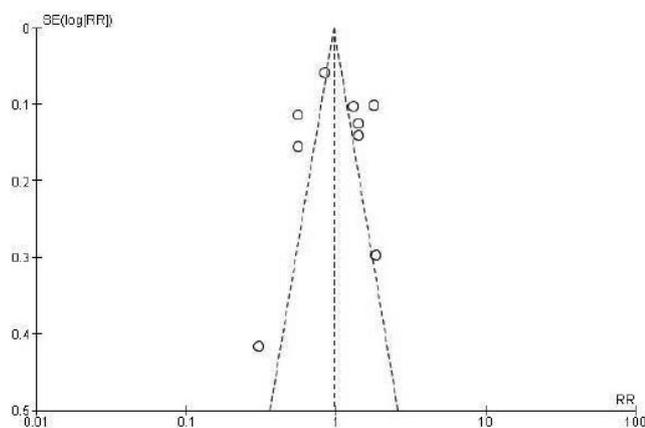
The patient data meta-analysis shown in this study has significant evidence to support their use in secondary prevention for people at risk of cardiovascular disease. This is especially true in reducing MACEs in the pre-pandemic era in forest plot Figure 2, with (RR: 0.68,  $p < 0.00001$ , 95% CI 0.67 – 0.70,  $I^2=92\%$ ). Similarly in Figure 3, statins proved significantly superior in reducing all-cause mortality outcome before the COVID-19 pandemic, with (RR: 0.82,  $p < 0.00001$ , 95% CI 0.78 – 0.86,  $I^2=48\%$ ).

Acute coronary syndrome (ACS), myocardial damage, arrhythmias, venous thromboembolism, and other cardiovascular problems appear to be made worse by COVID-19. It has been hypothesized that the high level of systemic inflammation linked to COVID-19 could hasten the onset of subclinical conditions or result in de novo cardiovascular damage.<sup>8</sup>

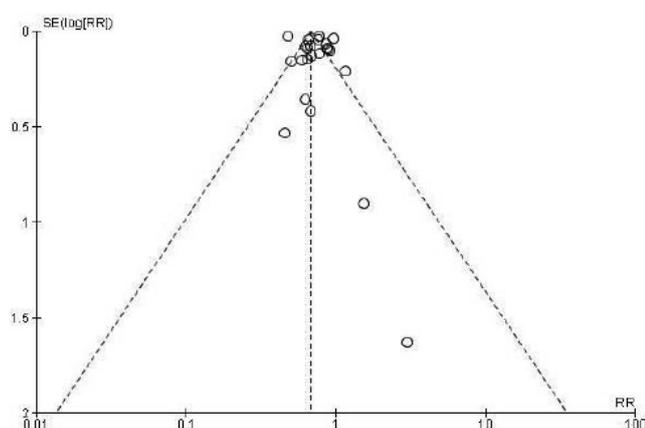
Additionally, COVID-19 victims' hearts had mild inflammation and viral RNA, according to autopsy studies and causes myocardial injury and myocarditis. Because of systemic inflammation or a cytokine storm, the mechanisms causing COVID 19-induced ACS may include plaque rupture, coronary spasm, or microthrombi. For instance, collagenases, which are secreted by activated macrophages and which break down collagen, a key component of the fibrous cap of atherosclerotic plaques, might cause plaque rupture. It is also known that activated macrophages release tissue factor, a strong procoagulant that causes thrombus development when the plaque bursts. The risk of thrombus development and ACS may also rise if SARSCoV-2 infection directly damages endothelium or vascular tissue. Furthermore, COVID-19-induced ACS and acute myocardial damage can exacerbate pre-existing heart disease or cause contractile dysfunction to manifest on heart failure. In the later stages of COVID-19, the immune system's reaction to the infection may cause the onset of stress-induced cardiomyopathy or cardiac dysfunction



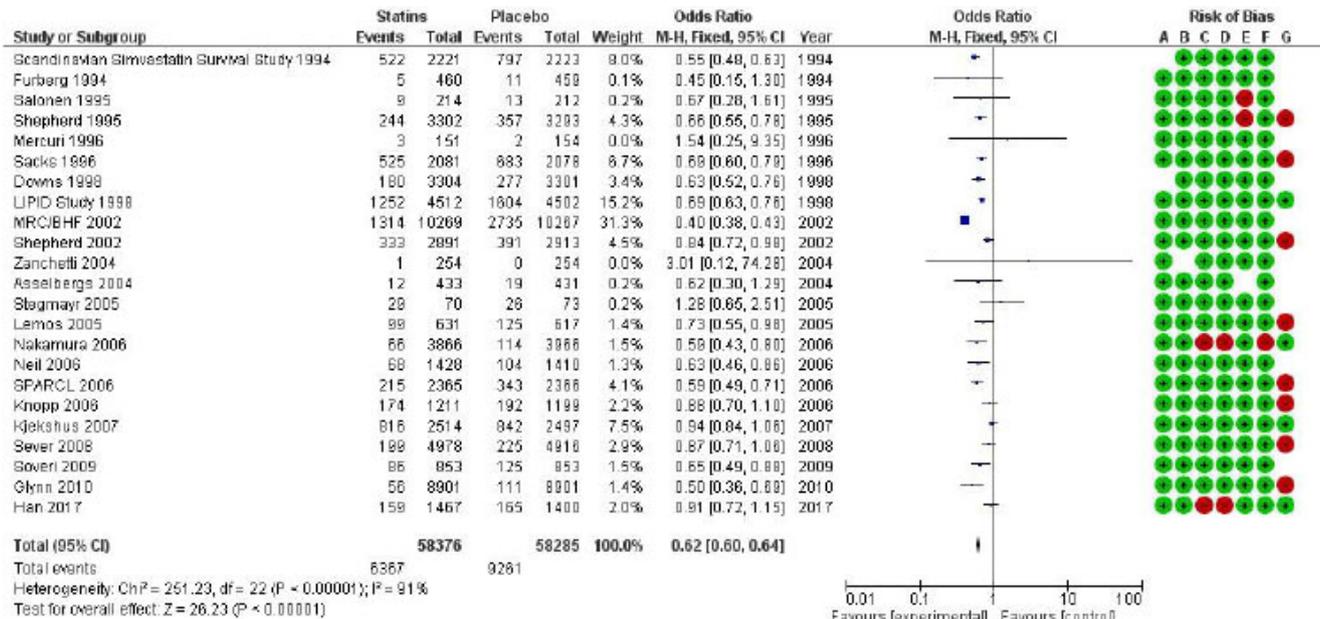
**Figure 2.** Funnel plot on the effect of statins versus placebo on MACEs outcome before the COVID-19 pandemic.



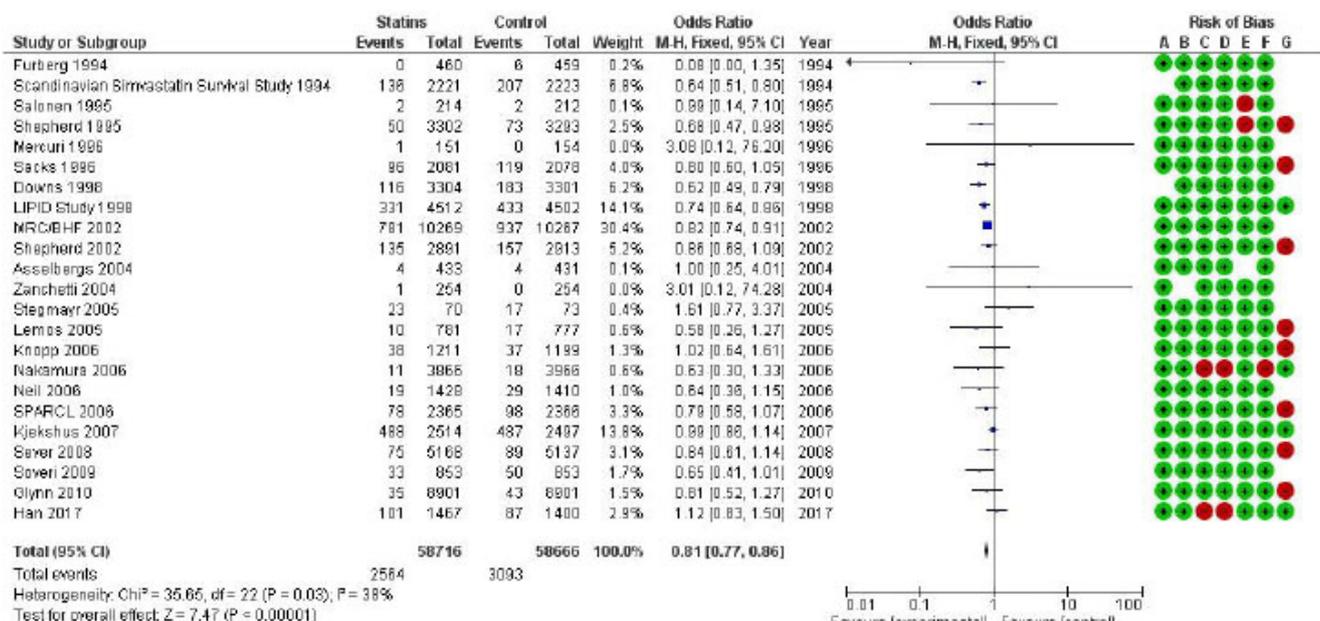
**Figure 3.** Funnel plot on the effect of statins versus placebo on all-cause mortality outcome before the COVID-19 pandemic.



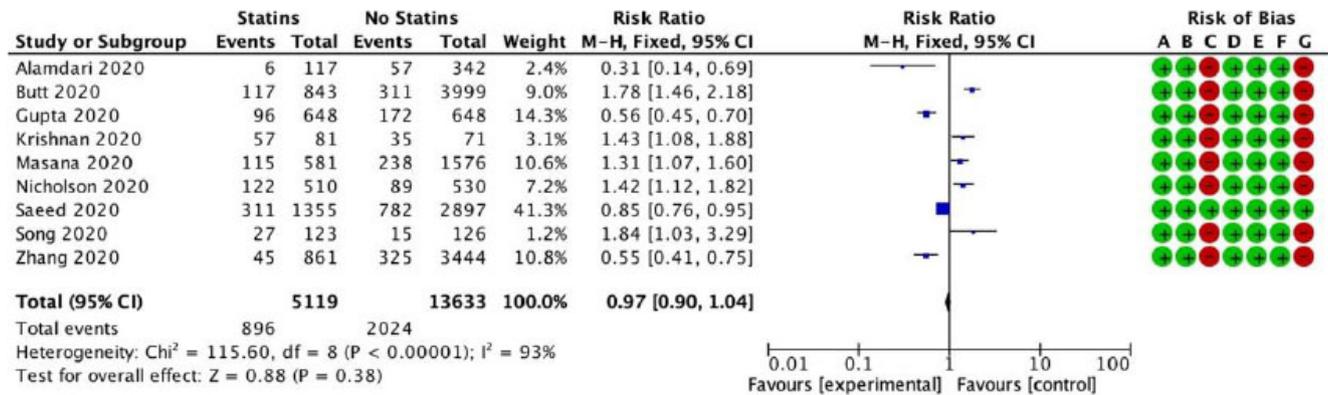
**Figure 4.** Funnel plot showing the effect of statins versus without statins on all-cause mortality outcome during the era of the COVID-19 pandemic.



**Figure 5.** Forest plot showing the effect of statins versus placebo on MACEs outcome before the COVID-19 pandemic with (RR: 0.62,  $p < 0.05$ , 95% CI 0.60 – 0.64,  $I^2 = 91\%$ ).



**Figure 6.** Forest plot showing the effect of statins versus placebo on all-cause mortality outcome before the COVID-19 pandemic with (RR: 0.81,  $p < 0.05$ , 95% CI 0.77 – 0.86,  $I^2 = 38\%$ ).



**Figure 7.** Forest plot showing the effect of statins versus without statins on all-cause mortality outcome during the era of the COVID-19 pandemic with (RR: 0.97,  $p < 0.05$ , 95% CI 0.90 – 1.04,  $I^2=93\%$ ).

caused by cytokines.<sup>8</sup>

During the COVID-19 pandemic, studies on statin use were also associated with improvement of clinical outcomes in patients with COVID-19. In the meanwhile, individuals with comorbidities and on statin therapy should always be advised to continue statin therapy despite the ongoing pandemic.<sup>57,58</sup> However, our limitations indicate that further clinical trial studies are needed to assess the benefits of statins on individuals with COVID-19 disease.<sup>59</sup> Patients who are at risk for cardiovascular diseases, associated with high cholesterol levels, need special attention.<sup>60</sup>

Primary Health Centers also referred as 'Puskesmas' in Indonesia have an important role here. Through the Integrated Service Post (Posbindu) program or the Elderly Integrated Service Post (Posyandu Lansia) program, patients are educated and encouraged to screen for non-communicable diseases, such as hypercholesterolemia, diabetes, and cardiovascular disease. That way, many patients who are at risk can be treated properly.

The limitation of this study is that there are no librarians who assist in compiling search string strategies. During the pandemic era, the studies that were obtained were still small. Another weakness in this study is also not listed in any registration. However, this study is evidence of medicine that it is very important to treat dyslipidemia comprehensively, especially in primary health facilities. Supported by homogeneous between-study variations and narrow precision statistical results.

## CONCLUSION

Statins have been shown to statistically reduce MACEs and all-cause mortality before the COVID-19 pandemic and further studies are needed during the pandemic. Government policies need to address the lack of screening for dyslipidemia and appropriate treatment in the primary care setting, especially during the pandemic.

## CONFLICT OF INTEREST

The authors declare no conflict of interests.

## ETHICS CONSIDERATION

This article was a review article therefore no ethical consideration has been made.

## FUNDING

The authors received no specific funding for this work.

## AUTHOR CONTRIBUTION

AJ and JAT were involved in the idea and design of the paper. Authors AJ, RM, JAT, RHP, IESU, DD, TC, BS and CMSN drafted the article; critically revised the text for key intellectual content; and approved the final version to be published. AJ and JAT were involved in the final approval of the published edition.

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